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Successful treatment of juvenile myelomonocytic leukemia relapsing post stem cell transplant using donor lymphocyte infusion

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TITLE PAGE

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ABSTRACT

Juvenile myelomonocytic leukaemia (JMML) is a rare paediatric malignancy. Haematopoietic stem cell transplant (SCT) is the only curative approach. However, relapse post SCT remains the major cause of treatment failure. Unlike most other paediatric malignancies, JMML maybe susceptible to a graft versus leukaemia (GVL) effect although unlike chronic myeloid leukaemia, reports of response to donor lymphocyte infusions (DLI) remain scanty. This is the first report that describes the successful treatment of relapsed JMML with DLI in the absence of further chemotherapy and provides definite proof of a GVL effect in JMML.

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INTRODUCTION

JMML is a rare disorder, accounting for about 2% of all childhood haematological malignancies^{1,2}. It includes a heterogeneous spectrum of myelodysplastic/myeloproliferative diseases, which has proved difficult to classify and segregate into distinct clinical syndromes. In 1997 an international consensus panel agreed common clinical and laboratory criteria to diagnose JMML³.

The initial course of JMML is varied with approximately one third of patients developing a rapidly progressive course leading to early death, yet occasional patients remain stable without any treatment¹. Hence although survival for 12 years after diagnosis without treatment has been described, the 10-year disease-free survival without SCT is only 6% and median survival time is approximately 10 months^{2,4}. Treatment of JMML with chemotherapy has been unsuccessful with no sustained response to even high dose chemotherapy protocols^{5,6}. Haematopoietic stem cell transplantation (SCT) has offered a chance of cure, but relapse rates and transplant related mortality remain higher than with other haematological malignancies^{4,7-9}. However, unlike most other paediatric leukaemias, JMML may be susceptible to a GVL effect with lower relapse rates following reduced graft versus host disease (GVHD) prophylaxis⁴, in the presence of acute GVHD^{7,8} and chronic GVHD^{10,11}. There are a few reports of post-SCT relapse of JMML responding to withdrawal of immunosuppression^{8,10,12} but there has been only one successful report of the use of DLI in this setting, and this was given in conjunction with further chemotherapy⁹. Here we describe a child who relapsed early post transplant, but has subsequently gone into long-term remission with the use of DLI without any further chemotherapy.

CASE HISTORY

A six-month-old girl presented with diarrhoea and vomiting, and bleeding from her right nipple. On assessment she had fallen from the fiftieth to the third centile for both height and weight, and was pale with marked hepatosplenomegaly. She was anaemic, had a leucocytosis with a monocyte count of $18.5 \times 10^9 /L$, and was mildly thrombocytopenic. A blood film revealed immature neutrophils and an increase in myelomonocytic cells, typical of a diagnosis of JMML. A bone marrow aspirate revealed a hypercellular marrow with mild dysplastic changes and 16% blast cells. Bone marrow cytogenetics revealed 84% of cells showing a 45 XY -7 karyotype. Haemoglobin electrophoresis revealed 7.3% HbF. Hypersensitivity to granulocyte macrophage colony stimulating factor and spontaneous colony formation was demonstrated in colony forming unit-granulocyte macrophage cultures.

Over the next few months, the white cell count remained stable, but she required two hospital admissions for respiratory infections and had continued failure to thrive. It was decided to treat with two cycles of high dose AML-type chemotherapy to de-bulk her disease prior to bone marrow transplant. Following recovery of blood counts, splenomegaly persisted and the blood film continued to show features of JMML.

1 month later (6 months after diagnosis) the patient underwent an unrelated donor SCT from a male donor fully matched at HLA A, B, C, DRB1, DQB1 loci. Conditioning consisted of, Campath 1H 1mg/kg, Busulphan 16mg/kg, Cyclophosphamide 120mg/kg, and Melphalan 140 mg/m². GvHD prophylaxis consisted of Methotrexate (15mg/m², 10mg/m², on days +3, +6 with Folinic acid rescue), and Cyclosporin. T replete bone marrow containing 16.6 x10⁶/kg CD 34 +ve cells and 1.2 x 10⁸/kg CD3 +ve cells were infused.

The immediate post transplant period was complicated by an episode of Pneumatosis Intestinalis. This was treated with 10 days of broad-spectrum antibiotics; nil by mouth and total parental nutrition and day +11 methotrexate was omitted. Neutrophil recovery to 0.5×10^9 occurred on day +14, and engraftment was confirmed by XY Fluorescent in situ hybridisation (FISH) on day +19 and found to be 100% donor in both mononuclear (MNC) and polymorphonuclear (PMN) cell fractions.

Cyclosporin was weaned to zero between days +26 and + 56 in an attempt to exploit a GVL effect. Grade I skin GVHD, not requiring treatment, occurred on day +40. The patient was discharged from hospital on day +48. On day +68, XY FISH on the blood showed recurrence of host haemopoiesis (5% in MNCs and 1.5% in PMNs). By day +102 this had progressed to 83 % host MNCs and 10 % host PMNs. Clinically she remained well, but her splenomegaly had increased and she was febrile. A blood film showed reappearance of abnormal monocytes and basophils although counts remained within the normal range. A repeat bone marrow aspirate was of normal appearance but FISH analysis revealed 52% of interphase cells to be Monosomy 7. A diagnosis of relapsed JMML was therefore made.

On day +114, the patient was given a DLI containing 1×10^8 CD3 +ve cells/kg. 10 days later she developed GvHD as manifested by a florid skin rash and abnormal liver function tests. She was given a brief course of steroids for one week for the GVHD. However her spleen continued to increase in size following DLI and she remained persistently febrile. An emergency splenectomy was performed 2 weeks post DLI for respiratory compromise and malignant hypersplenism; respiratory symptoms improved and fever resolved promptly. On day 24 post DLI she became profoundly neutropenic. A bone marrow aspirate at this stage was acellular but with no evidence of disease. She was started on G-CSF, which was given for one week after which counts normalised.

By day +35 post DLI she was back at 100% donor MNCs and PMNs (see Fig 1). Her cutaneous GvHD had improved (now grade 1) and her liver function tests were normal. At 17 months post DLI she remains well, continues to thrive and has 100% donor chimaerism, and no residual GvHD. Her blood counts have been normal for the last 15 months and her most recent blood counts show haemoglobin of 11.0g/dl; white cell count of $11.85 \times 10^9/l$ (neutrophils $5.10 \times 10^9/l$, lymphocytes $5.81 \times 10^9/l$, monocytes $0.47 \times 10^9/l$) and a platelet count of $601 \times 10^9/l$.

RESULTS AND DISCUSSION

Relapse of JMML post SCT remains the major cause of treatment failure. This report describes the first response of relapsed JMML to DLI in the absence of further chemotherapy, and provides definite proof of a GVL effect in JMML. The anti-leukaemia effect of GvHD is well documented in acute and chronic leukaemia¹³⁻¹⁵. DLI has been particularly successful in the treatment of chronic myeloid leukaemia, where induction of a GVL effect has led to subsequent disease remission in 73% of patients^{16, 17}. Matthes-Martin et al⁹ have described the use of DLI for relapsed JMML previously in two cases. In the first case DLI (1×10^7 CD3⁺ cells) was unsuccessful and the child underwent a second transplant from which she developed grade IV GvHD, but remains in long term remission. The second child relapsed on day +68 post T- cell replete unrelated donor transplant and did not respond to withdrawal of immunosuppression. Subsequently the child underwent splenectomy and received 6-Mercaptopurine, followed by two DLIs of 5×10^5 and 1×10^6 CD3⁺ cells. This patient remained in complete remission 9 months later. This case has striking similarities to ours. The patient also had monosomy 7, received a transplant from an unrelated donor, developed only minimal GvHD post transplant and was treated with a debulking splenectomy and DLI after relapse; the only difference being the addition of further chemotherapy in the previous case. It is interesting that the only 2 patients responding to DLI had monosomy 7; despite the fact only 24-29 % of patients with JMML have this karyotype^{2,5}. Monosomy 7 is a poor prognostic marker in AML/MDS¹⁸ but probably not in JMML¹⁹

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Figure 1

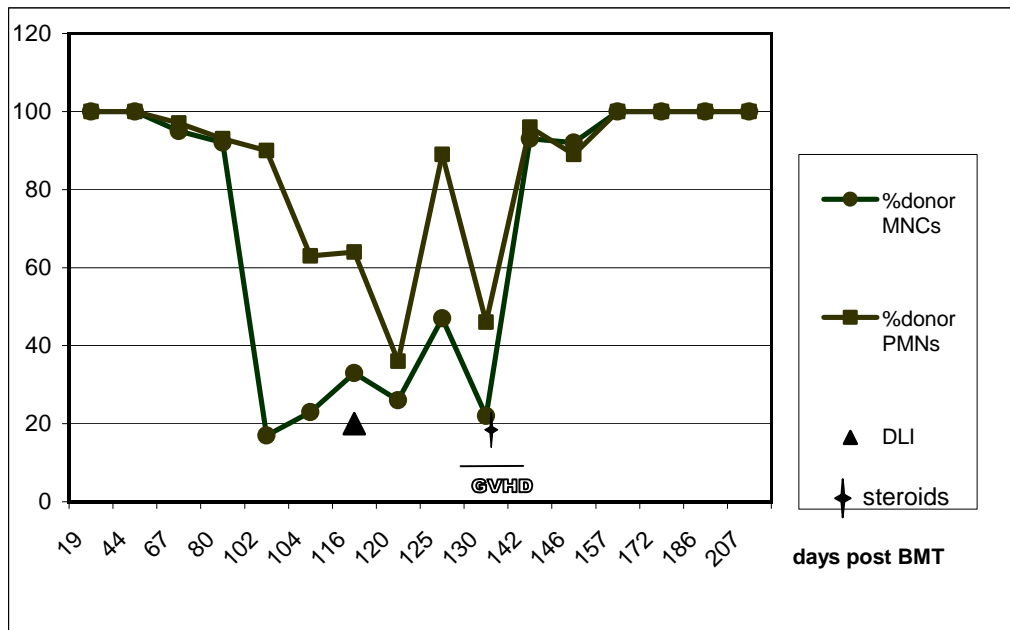


FIGURE LEGEND

This graph depicts the fall in donor chimaerism at relapse of JMML post transplant and the response to DLI with prompt and sustained return to donor chimaerism. This patient initially had recurrence of host haemopoiesis at day 68 post transplant. By day +102 this had progressed to 83% host MNCs and 10% host PMNs. DLI was given on day 114. GvHD that followed the DLI was treated with steroids for one week from day +138 to day +145. By day 35 following the DLI (day 148 post transplant) there was return to 100% donor chimaerism and the patient remains well and disease free 17 months post transplant.